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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,299	07/11/2003	James G. Barsoum	A123 CON	6907

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,299	BARSOUM ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,34,35,38,39,41,42,44,46,52,53 and 55-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 34, 35, 38, 39, 41, 42, 44, 46, 52, 53, and 55-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendments of 3/20/07 has been entered.

Claims 1, 34, 35, 38, 39, 41, 44, 46, 52, and 53 have been amended.

Claims 36, 37, 43, and 54 have been cancelled.

Claims 55-56 are newly presented.

Claims 1, 34, 35, 38, 39, 41, 42, 44, 46, 52, 53, and 55-66 are presently pending and considered.

Claim Status, Cancelled Claims

In light of Applicant's cancellation of claims 36, 37, 43, and 54, all objections and/or rejections of such claims are rendered moot, and thus are withdrawn.

Claim Rejections - 35 USC § 112 – clarity

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of the amendments to Claims 38, 44, and 46, the rejections to such claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

To wit, Claim 38 now limits both vectors to adenoviral vectors, Claim 44 limits the first vector properly, and Claim 46 now requires both vectors to be replication defective.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the amendments, the rejections of Claims 1, 34-36, 38-39, 41-44, 46, and 52-54 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To wit, Applicant's scope has been changed sufficiently to remove the general exemption within the method.

Claim Rejections - 35 USC § 112 – new matter

Claims 58-66 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 58-66 encompass generic compositions comprising a generic viral vector encoding a therapeutic protein operably linked to a promoter functional in hepatocytes, and a generic liposome-encapsulated cytotoxin.

The only support for such compositions and methods found in the specification relating to such genera is the single species of liposome-encapsulated doxorubicin (e.g., pp. 14-15, paragraph bridging).

Still further, while the Art of record demonstrates a knowledge that liposome-encapsulated cytotoxic drugs will target and kill kupffer cells when administered through specific routes (e.g., Official Action of 9/18/06, p. 13), and hence, within the knowledge disclosed by the Examiner in the prosecution, such would be a method to specifically target and kill kupffer cells, obviousness does not supplant the need to demonstrate, either through explicit or implicit disclosure, that Applicant possessed the genera presently claimed.

Given that the only disclosure, both explicit (specification, pp. 14-15, paragraph bridging), and implicit (EXAMPLES), is that liposome-encapsulated doxorubicin may be used, the Artisan could not reasonably determine that Applicant possessed the genera presently claimed at the time of invention.

Hence, these claims are properly rejected for comprising new matter.

Response to Argument – written description, liposomal cytotoxins

Applicant's argument of 3/20/07 has been fully considered but is not found persuasive.

Applicant cites several references to the specification to argue that support is found (p. 9, paragraph 2).

Such is not persuasive. As is shown above, such references simply demonstrate liposomally encapsulated doxorubicin.

Claims 1, 34, 35, 38, 39, 41, 42, 44, 46, 52, 53, and 55-66 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims encompass a generic promoter functional in hepatocytes.

The Examiner has found no support for such limitation, either explicit or implicit, in the originally-filed specification and claims. Moreover, Applicant's support is limited to a single paragraph, reciting tissue specific promoters (Applicant's argument of 3/20/07, p. 9, paragraph 3, citing the specification, pp. 9-10, paragraph bridging). However, such does not provide sufficient support for promoters functional in a hepatocyte, as such would necessarily an obvious species within the genera of tissue specific promoters.

Moreover, nothing in the Art of record indicates that such promoters would be the promoter of choice, and hence, the Art does not contribute anything over the disclosure in the specification and claims as filed.

Hence, these claims are properly rejected for comprising new matter.

Comment – New Matter and non-conjugated agent/vector compositions

It is noted that newly amended claims 52, 53, and 55 now contain the limitation "wherein said first viral vector and said agent are not conjugated". In order to maintain a

clear record, the Examiner notes that Applicant did have possession of the invention claimed, as an inherent property of the compositions and methods.

To wit, the confluence of the specification discusses the viruses and agents in general and never discusses that these substances may be conjugated. Moreover, the confluence of the specification teaches that the agent inhibits Kupffer cell uptake of the viral vector comprising the transgene. Moreover, for those embodiments of separate administrations of such, a single composition wherein these two substances are chemically linked is simply not enabled to practice separate administrations. Finally, for concurrent administrations, if the substances were linked, the Kupffer cells would uptake the agent, as well as the virus vector, as they are linked, and the end result would not be increased expression in the liver, but simple sequestration by the Kupffer cells, and as such, the amount of expression would be no different from the absence of the agent.

Therefore, the Examiner considers this limitation to be inherent in the compositions as disclosed, and further, that the Artisan would have understood Applicant to have been in possession of the limitation as claimed.

Claim Rejections - 35 USC § 112 – written description

In light of the amendments, the rejections of Claims 1, 34-39, 41-44, 46, and 52-54 remain under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn.

Specifically, the claims now are limited to agents that are virus vectors or liposomally-encapsulated cytotoxins, and not generic agents with characteristics which are in common with virus vectors or cytotoxins.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 34-39, 41-44, 46, 52-54 are and/or remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of increasing hepatocyte expression of a therapeutic gene product, wherein the second viral vector or the liposome encapsulated cytotoxin reaches the liver prior to or at the same time as the first viral vector and expression is increased in the liver over that of administrations without the agent, does not reasonably provide enablement for increasing gene product levels in any tissue other than liver, or for viral vectors chemically conjugated to the agent, for reasons of record and/or necessitated by amendment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Several bases of rejection have been withdrawn in light of the amendments, including (i) the breadth of agents, (ii) non-equivalent viral vector types, (iii) the breadth of promoters, and (iv) agents other than adenoviral vectors or cytotoxins. These have been withdrawn for the following reasons, respectively: (i) the agents are now limited to liposome-encapsulated cytotoxins, or viral vectors, (ii) the limitation to the same of vector as the agent as is used to deliver the transgene, (iii) promoters limited to hepatocyte expression, and (iv) the demonstration that adenoviral vectors are filtered by

the liver kupffer cells regardless of their tropism and the absence of any art demonstrating that other viral vectors are not similarly filtered by kupffer cells, as well as the knowledge in the art that liposome encapsulated cytotoxins target kupffer cells.

Still further, for the record it is stressed that it is well known that kupffer cells filter out viruses entering the liver and passing through the blood stream through the liver, and it is logical that a specific virus's method of sequestration by Kupffer cells is necessarily saturable, as such is simple thermodynamics. And hence, it is scientifically in agreement that a saturation by a preadministered virus would necessarily be able to saturate its own mechanism of entry, precluding subsequent virus from being sequestered. Still further, if the viruses both reach the Kupffer cells at the same time, some of the second virus will necessarily perform some of the sequestration, thereby increasing the amount of first vector able to reach other cells. As such, the method is enabled for this aspect.

However, from the amendment, by not adding a conclusion requiring increased expression in the liver, but simply providing a generalized increased expression in the subject, it is clear that the claims are specifically meant to encompass increased expression in any tissue. However, for reasons of record, this is not reasonably predictable, as (i) if the vector enters the liver, it is either (a) filtered out by the Kupffer cells, or (b) infects the hepatocytes, and as such, it is not reasonably predictable that any vector will reach other tissues. Secondly, even Applicant's own data in the non-patent literature fails to find that any other tissue is affected with increased expression but only a minimal expression in the spleen, and even after the removal of the spleen no other expression is seen (Tao, et al. (2001) Molecular Therapy, 3(1): 28-35, e.g., p. 32, of

record). Still further, several more arguments are present on the record (e.g., Official Action of 9/18/06, pp. 11-12). Such arguments have been made on the record previously.

Lastly, with chemically conjugated vectors, it is noted that Applicant's new claim terminology of Claim 52, indicates that the other claimed methods and compositions are to encompass conjugated agent and vector, for the simultaneous administrations. However, such is not enabled as the conjugation would simply cause increased uptake by the Kupffer cells, and therefore would necessarily increase transgene expression levels in the liver, as the Kupffer cells would sequester such vectors similarly to administrations without the agent.

Response to Argument – Enablement

Applicant's argument of 3/20/07 has been fully considered but is not found persuasive.

Applicant argues that the argument of the Examiner is that not any form of administration would allow the vectors to reach the liver, and by limiting the claims to achieving entry into the liver, Applicant has necessarily removed those embodiments that do not work (p. 17).

Such is not persuasive. Applicant has claimed that the vector reaches the liver, and then attempts to encompass expression in other tissues. As noted above, Applicant's own data published in the NPL indicates that other tissues are not effected, even when administration is by IV, which is known to deliver directly to the liver the highest amount possible.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 52, 53 and 55 remain and/or are newly rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 6,001,557 to Wilson et al., for reasons necessitated by the amendments.

While it is noted that the specific citation of claims indicates that the adenoviruses are conjugated, the following new explanation is provided.

Wilson teaches production of adenoviruses by co-transfection of a shuttle vector containing the therapeutic minigene and missing essential genes, and a helper virus, carrying the genes required for production of virus, which may or may not be designed to be packaged efficiently (col. 5, paragraph 6). With regard to promoters active in the liver, the CMV promoter is taught, and such is functional in the liver (e.g., col. 8, paragraph 1).

With regard to Claims 52 and 55, such adenoviruses anticipate the claims, as they are in water.

With regard to Claim 53, the production of viral particles, when using the helper virus that is capable of being packaged, will necessarily produce the viral particles.

Hence, the claims are anticipated.

Response to Argument – anticipation, Wilson

Applicant's argument of 3/20/07 has been fully considered but is not found persuasive.

Applicant's argument is limited to the claim terminology and its required "conjugation" of the viruses (p. 18).

Such is not persuasive. As noted above, other bases of rejection now may be applied from the same reference.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 38, 43, 52, 53 and 54 remain and/or are newly rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 6,730,507 to Graham, et al., for reasons necessitated by amendment.

The claims are now limited to the second vector not comprising the therapeutic transgene of the first vector. Also, use of promoters functional in liver now limit the claims.

However, Graham teaches that the sequential administrations of adenoviral vectors may comprise distinct transgenes (e.g., col. 12, paragraph 2), as well as the use of the CMV promoter (e.g., FIGURE 1).

Hence, even with the new limitations, these claims are anticipated.

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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